REMARKS/ARGUMENTS

Claims 1-16 are pending in the above-referenced application. Claims 1 and 8-11 have been withdrawn from consideration.

Claims 2-6 have been amended to further define the Applicant's invention. Claim 7 has been amended to be consistent with the specification. No new matter has been added.

This is a response to the final Office Action dated September 01, 2010 wherein the Examiner rejected: (1) the specification as failing to provide proper antecedent basis for the claimed subject matter; (2) claims 2, 5-7 and 12-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; (3) claim 6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; and (4) claims 2-7 and 12-16 under 35 U.S.C. 103(a) as being unpatentable over EP 391396 (Simon) in view of the "Effects of Postnatal Estradiol and Progesterone Replacement in Extremely Preterm Infants," *The Journal of Clinical Endrocinology & Metabolism*, December 1999 (Trotter)..

Applicant respectfully thanks the Examiner for the time and effort in preparing and issuing the instant Action.

In view of the foregoing amended claims and the remarks that follow, reconsideration of the rejections and a notice of allowance are respectfully solicited.

Objection to the Specification

The Examiner objected to the specification for failing to provide proper antecedent basis for the claimed subject matter as recited in claim 7. Claim 7 has been amended as indicated above to be consistent with the specification. In view of the amendment, rescission of the objection is respectfully solicited.

§ 112 Rejection, second paragraph Rejection of claims 2, 5-7, and 12-16

Claims 2, 5-7 and 12-16 are rejected under 35 U.S.C 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 is separately rejected under 35 U.S.C 112, second paragraph, for reciting a broad range together with a narrow range.

Independent claim 2 and dependent claims 5, 6 and 7 have been amended as indicated above. In view of the amendment, rescission of the indefiniteness rejection is respectfully solicited.

§ 103(a) Rejection of Claims 2-7 and 12-16 over Simon et al in view of Trotter

Claims 2-7 and 12-16 are rejected under 35 U.S.C § 103(a) as being unpatentable over Simon et al in view of Trotter.

In rejecting the foregoing claims, the Examiner relies on Simon to "teach medicinal oil-in-water emulsions comprising an effective amount of a lipophilic drug". The Examiner alleges that Simon teaches all of the elements of the claimed oil emulsion, except Simon does not teach an emulsion containing progesterone and an estrogen. (Office Action, page 7)

Of the rejected claims, amended Claim 2 recites:

> 2. (Currently Amended) A hormone-containing isotonic oil emulsion for intravenous administration comprising:
> at least one progestagen and at least one estrogen;
> an oil phase;
> an antioxidant;
> an emulsifier; and
> an aqueous phase;
> wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase.

Thus, amended claim 2 is directed to an oil emulsion for intravenous administration comprising, among other things, at least one progestagen and at least one estrogen, an oil phase; an antioxidant; an emulsifier and an aqueous phase. Claim 2 further specifies that the at least one progestagen and the at least one estrogen are dissolved in the oil phase prior to being mixed with the aqueous phase.

The '369 Simon publication is directed to a pharmaceutical composition suitable for the administration of hydrophobic drugs (page 5, lines 3), including lipophilic drugs such as amphotericin B, narcotic drugs such as morphine-base drugs, hydrophobic benzodiazepines such as diazepam, lipophilic steroids such as progesterone and testosterone propionate, lipophilic polypeptides such as cyclosporine (page 5, lines 4-10). The composition further comprises an oily carrier consisting of MCT oil optionally in combination with vegetable oil, a phospholipid, non-ionic and ionic surfactants and optionally an anti-oxidant such as α-tocopherol (Abstract, page 4, line 22 to page 5, line 2).

Simon teaches that the composition may be prepared by a number of ways. In one preparation mode, Simon teaches preparing an aqueous solution and an oily solution separately (page 5, lines 23-17) and mixing one with the other (page 5, lines 24 and 34). The aqueous solution comprises the non-ionic and ionic surfactants, the phospholipid and the oily solution comprises the oily carrier, the hydrophobic drug and the optional antioxidant (page 5, lines 24-27). Simon further teaches an "inventive mode" (page 5, line 54), wherein a liposome mixture and an oily mixture are prepared separately and subsequently mixed together. This inventive mode is suitable for the preparation of compositions in which the drug is both hydrophobic and has poor oil solubility (page 5, lines 55-57). The liposome mixture is prepared by mixing the phospholipid, the non ionic and ionic surfactants, and the drug if it is hydrophobic and has poor oil solubility (page 6, line 5-8). The oily mixture comprises the oily carrier and the optional anti-oxidant. If the drug is lipophilic, it is included in the oily mixture instead of the liposome mixture (page 6, lines 10-11). Thus, Simon teaches that depending on the hydrophobicity and oil solubility of the drug, it needs to be added to either the oily mixture or the liposome mixture.

As acknowledged by the Examiner, Simon does not teach an emulsion comprising progesterone and an estrogen. The Examiner relies on Trotter et al. to teach an oil-in water emulsion comprising estradiol (an estrogen) and pregn-4-ene-3, 20-dione (progesterone, a progestagen). (Office Action, page 7).

Trotter et al. describe a hormone replacement solution for use in extremely preterm infants (Abstract). Trotter teaches diluting 17-β-estradiol and progesterone in 98% ethanol and mixing the solution with a phospholipid-stabilized soybean oil emulsion such as Intralipid (Pharmacia & Upjohn, Inc.) for parenteral administration (page 4532, first column, last paragraph). Intralipid[1] from Pharmacia & Upjohn contains purified soybean oil, purified egg phospholipids, glycerol in water. As described, the hormones 17-β-estradiol and progesterone are diluted in 98% ethanol before being added to Intralipid. Thus, Trotter specifically teaches dissolving estradiol and progesterone in an aqueous phase (98% ethanol) before mixing the solution with Intralipid.

By teaching dissolving the hormones estradiol and progestagone in 98% ethanol before adding it to the oil phase (Intralipid), Trotter teaches away from the claimed emulsion, which recites "wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase **prior** to being mixed with the aqueous phase" (emphasis added). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. In *re Gurley*, 27 F. 3d 551, 553 (Fed. Cir. 1994)". Even though the Examiner merely relies on Trotter to disclose an estrogen, "a prior art reference must be considered in its entirely, i.e., as a whole, including portions that would lead away from the claimed invention" (§ MPEP 2141.02 (VI)). As Trotter teaches away from the claimed emulsion, Trotter cannot be combined with any other references to render the claimed emulsion obvious, as "[i]t is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)." § MPEP 2145. Therefore, the combination of Simon and Trotter is defective.

Furthermore, even if erroneously combined, the combination of Simon and Trotter still fails to disclose all of the elements of claim 2. As set forth above, among other things, Simon does not disclose an oil in water emulsion comprising at least one progestagen **and** at least one

[1] http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20I)/INTRALIPID.html

estrogen, wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase **prior** to being mixed with the aqueous phase. In disclosing a hormone replacement solution comprising an estrogen and progesterone, Trotter specifically teaches dissolving 17-β-estradiol and progesterone in an aqueous solution of 98% ethanol **before** mixing with Intralipid. Thus, even if erroneously combined, Simon in view of Trotter does not disclose a hormone-containing isotonic oil emulsion comprising at least one progestagen and at least one estrogen, wherein the at least one progestagen and the at least one estrogen are dissolved in the oil phase **prior** to being mixed with the aqueous phase, as recited in part by claim 2.

Furthermore, Applicant respectfully submits that a skilled person in the art would not have been motivated to ignore the teachings of the cited references and arbitrarily dissolve Trotter's estradiol into Simon's oil phase to arrive at the claimed emulsion. Indeed, as characterized by the Reference Table published by U.S. Pharmacopeia [2], estradiol is "practically insoluble in water, **soluble in alcohol**, in acetone, in dioxane, in chloroform, and in solutions or fixed alkali hydroxide; **sparingly soluble in vegetable oils**" (emphasis added). As set forth above, Trotter specifically teaches dissolving estradiol in 98% alcohol (Trotter, page 4532, first column, last paragraph). Simon specifically teaches dissolving a drug which has poor oil solubility, **not** in an oil phase, but in a liposome phase (Simon, page 6, line 7). Therefore, a skilled artisan would **not** have been motivated to modify both the teachings of Simon and Trotter to dissolve estradiol in an oil phase, given that estradiol is known to be readily soluble in alcohol but have poor oil solubility. Thus, contrary to the Examiner's contention, a skilled artisan would not have been motivated to combine Simon with Trotter to produce the claimed emulsion.

In view of the foregoing, Applicant respectfully submits that the Trotter publication is not combinable with the '369 Simon publication to render the claimed emulsion obvious under § 103(a) since among other things, Trotter teaches away from the claimed emulsion. Thus, the combination of the cited references is defective. Even if erroneously combined, the cited references still fail to disclose all of the elements of the claimed emulsion. Furthermore, a

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http://www.pharmacopeia.cn/v29240/usp29nf24s0_alpha-2-14.html

skilled artisan would not have been motivated to modify both the teachings of Simon and Trotter to dissolve estradiol in an oil phase to produce the claimed emulsion.

For at least the reasons set forth above, Applicant respectfully submits that the cited references of Simon and Trotter fail to render claim 2 obvious under § 103(a). Since claims 3-7 and 12-16 depend from claim 2, they too are allowable over the cited reference for at least the same reasons.

CONCLUSION

In view of the foregoing arguments, Applicant respectfully submits that claims 2-7 and 12-16 are patentable and allowance is respectfully solicited.

Should the Examiner wish to speak with Applicant's agent, she is invited to contact the undersigned at the telephone number identified below.

Respectfully submitted,
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